International Journal of Cardiology 152 (2011) 162–170

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Cardiac ion channel mutations in the sudden infant death syndrome

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ARTICLE INFO

Article history:
Received 14 September 2010
Received in revised form 27 November 2010
Accepted 8 December 2010
Available online 6 January 2011

Keywords:
Sudden infant death
Ion channelopathies
Long QT syndrome
Short QT syndrome
Brugada syndrome

ABSTRACT

Sudden infant death syndrome (SIDS) is characterized by the sudden death of an infant that occurs during sleep and remains unexplained despite thorough examination. In addition to clinical associations such as prone sleeping and exposure to cigarette smoke, several genetic factors have been identified with regard to SIDS, including autonomic disorders, immunologic polymorphisms and metabolic disorders. In the past decade, postmortem genetic analysis ('molecular autopsy') of SIDS cases has revealed a number of cardiac ion channel mutations that are associated with arrhythmia syndromes, including the long QT syndrome, Brugada syndrome and short QT syndrome. Mutations have been found in genes encoding (subunits of) cardiac potassium, sodium and calcium channels, as well as in genes involved in the trafficking or regulation of these channels. Here, we review the literature on cardiac ion channel mutations in relation to SIDS. Combining data from population-based cohort studies, we conclude that at least one out of five SIDS victims carries a mutation in a cardiac ion channel-related gene and that the majority of these mutations are of a known malignant phenotype. Genetic analysis is therefore recommended in cases of sudden infant death. More research is required to further elucidate the pathophysiology of SIDS and to determine whether genetic or electrocardiographic screening of apparently healthy infants should be pursued.

1. Introduction

The term 'sudden infant death syndrome' (SIDS) was first proposed in 1969, to describe "the sudden death of any infant or young child which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death" [1]. Several reconsiderations led to further specification of this definition, limiting the victim's age to <1 year, specifying that death apparently occurred during sleep and stating that thorough examination should include complete autopsy and review of the death scene and clinical history [2]. Also, it has been proposed to classify SIDS cases into different categories according to their features and documentation [2]. Despite these attempts, the definitions and protocols used for diagnosing SIDS have never been fully standardized, and SIDS still remains a diagnosis of exclusion [3].

The prevalence of SIDS has decreased considerably since the 1992 American Academy of Pediatrics recommendation to avoid for babies to sleep in the prone position, and the subsequent international 'Back to Sleep' campaign [4]. Nevertheless, SIDS has until today remained a major cause of infant mortality in developed countries. Accounting for over 2100 deaths, it was the third most important cause of infant mortality in the United States in 2007 [5].

Despite its relatively high prevalence, the exact pathophysiology of SIDS is still poorly understood. Many mechanisms have been suggested and investigated, including infections and several genetic abnormalities. Presumably, SIDS is a multifactorial disorder, with multiple mechanisms resulting in or predisposing to its development. This reinforces the relevance of the search for preventable causes. In line with the presumed multifactorial nature of SIDS, several 'triple risk' hypotheses—with three risk factors contributing to SIDS, e.g. a vulnerable infant, a critical developmental period in homeostatic control, and an exogenous stressor—have been proposed, but none of these have significantly improved our understanding of the cause of SIDS [6].

In this paper, our main aim is to review the literature in which cardiac ion channel mutations are described as a possible cause or predisposing factor of SIDS. Additionally, we will first give a brief overview of several clinical associations and non-cardiac genetic factors that have been reported with regard to SIDS.

2. Clinical associations

Risk factors for SIDS include male gender, age two to four months, prematurity, low birth weight, poor prenatal medical care, low socioeconomic status of the family, young age of parents, parental low educational level, short periods between pregnancies, multiple pregnancy, drug intake by pregnant woman, winter months, prone

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0167-5273/
doi:10.1016/j.ijcard.2010.12.051

sleeping, exposure to cigarette smoke during pregnancy and after birth, and overheating [3]. Most deaths occur during the night and early morning [7]. Additionally, epidemiological studies have reported ethnic differences in the incidence of SIDS; it is significantly higher among indigenous groups than among non-indigenous groups from the same countries [8]. These variations were found to be associated with both genetic and environmental factors.

Already in the 1960s, infections were proposed to contribute to the etiology of sudden unexpected infant death [9], and substantial evidence has since then become available to support this hypothesis. Inflammatory changes are commonly found in SIDS cases, and mild viral infection is an established risk factor for SIDS [7,10]. Several studies have shown that the incidence of SIDS varies in correlation to the incidence of infectious diseases, both on seasonal and yearly bases [10,11]. Among the pathogens that have been specifically reported in association with SIDS are *Staphylococcus aureus*, streptococci and *Escherichia coli* [7].

Additionally, some established risk factors for SIDS are reported to parallel risk factors for susceptibility of infants to infection. These include ethnicity, male gender, prone sleeping, cigarette smoke exposure, overheating, mild respiratory infections, lack of breastfeeding and poor socioeconomic conditions [7].

3. Non-cardiac genetic factors

3.1. Immunologic polymorphisms

The current most popular hypothesis on the mechanism by which infections provoke SIDS, is that pathogenic toxins give rise to an overwhelming pro-inflammatory cytokine response, ultimately causing physiological changes that lead to death [7]. This hypothesis is supported by the observation that several immunologic polymorphisms which facilitate uncontrolled inflammatory responses are found at a higher proportion in SIDS victims than in controls. Among the altered inflammatory responses that have been suggested to be associated with SIDS, are underproduction of the anti-inflammatory cytokine interleukin-10 (IL-10), overexpression of the powerful cytokines IL-1β and IL-6, and elevated vascular endothelial growth factor (VEGF) [7,10]. Altered cytokine responses have also been hypothesized to be the mechanism by which exposure to cigarette smoke predisposes to SIDS [7].

3.2. Autonomic disorders

Several structural and neurotransmitter alterations in the brainstem, consistent with impaired autonomic regulation, have been found in cases of SIDS [12]. These alterations include serotonergic abnormalities in the medulla oblongata [12–14]. Serotonin is a widespread neurotransmitter involved in many functions of the central nervous system, including respiratory and cardiovascular regulation. It has been hypothesized that the mechanism by which serotonergic dysfunction leads to SIDS, is through failure of protective respiratory and autonomic responses to life-threatening hypoxia or hypercapnia during sleep [12,13].

Genetic analyses have identified polymorphisms in the variable tandem repeat sequence in the promoter region of the serotonin transporter (5-HTT) gene. SIDS victims are more likely than matched controls to have the long allele of this gene [15,16]. Increasing effectiveness of the promoter and therefore of serotonin re-uptake by the serotonin transporter, this allele facilitates decreased serotonin concentrations at nerve endings.

Further genetic factors have been identified. Weese-Mayer et al. [17] analyzed several genes pertinent to early embryologic development of the autonomic nervous system. They identified rare protein-changing polymorphisms in association with SIDS in five genes (*PHOX2a*, *RET*, *ECE1*, *TLX3* and *EN1*). After investigating left ventricular and blood samples from nine SIDS cases, Livolsi et al. [18] reported cholinergic abnormalities in the intracardiac part of the autonomic nervous system. Compared with controls, SIDS cases showed an increase in both the density of cardiac muscarinic receptors and the erythrocyte acetylcholinesterase enzyme activity.

3.3. Metabolic disorders

In 1976, Sinclair-Smith et al. [19] were the first to investigate the ribs, livers and thymi of children who died of SIDS. In over 90% of 200 SIDS cases, the costochondral junction indicated that death was preceded by retardation in growth velocity. Additionally, 90% of livers showed fatty change indicating a metabolic upset, which in 5% was of severe degree. Postmortem biochemical screening of 313 livers from SIDS cases by Boles et al. [20], implicated abnormalities in several distinct fatty acid oxidation pathways in 14 infants (4.4%).

A well-investigated metabolic disorder studied in relation to SIDS is medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. This relatively common autosomal recessive inherited disease results from a deficiency in the enzyme which catalyzes the first step in β-oxidation of fatty acids. At least nine studies investigated SIDS populations with regard to p.A985G, the most prevalent mutation causing MCAD deficiency [21]. Overall, p.A985G heterozygosity was found in only 0.54% of 2587 SIDS cases, compared with 0.84% of 4636 control cases.

The fact that low birth weight, which is a risk factor for SIDS, is associated with hypoglycemia, has triggered investigation of gene polymorphisms in two key enzymes in blood glucose homeostasis: glucokinase (GK) and hepatic glucose-6-phosphatase (G6PC1). Whereas low G6PC1 expression and activity were found in some SIDS victims [22–24], no significant alterations have yet been identified regarding GK [23].

4. Cardiac genetic factors

Already in 1976, the long QT syndrome (LQTS) was proposed as a possible cause of SIDS [25,26]. LQTS is characterized by delayed cardiac repolarization, resulting in QT prolongation on the electrocardiogram (ECG) and a predisposition to syncope, seizures and sudden cardiac death [27,28]. These clinical features are caused by episodic polymorphic ventricular tachyarrhythmias such as Torsades de Pointes (TdP). Especially in young people, LQTS is an important cause of unexpected death. All features of LQTS, including a negative postmortem examination, are compatible with SIDS. In many cases, LQTS is an inherited disorder, caused by mutations in genes predominantly encoding subunits of cardiac ion channels [27,28].

At the cellular level, LQTS is characterized by an increase in action potential duration, as illustrated in Fig. 1A, which may result from an increase in inward current during the plateau phase of the action potential (AP), e.g. due to an increase in the late component of the fast sodium current (I_{Na}; 'gain of function'), or a decrease in outward current, e.g. due to a decrease in the rapid or slow delayed rectifier potassium current (I_{Kr} and I_{Ks}, respectively; 'loss of function').

Mutations in cardiac ion channel genes may also lead to the Brugada syndrome (BrS) and the short QT syndrome (SQTS) [29,30], which share several clinical features with LQTS, such as a predisposition to sudden cardiac death. The Brugada syndrome is characterized by changes in the ST segment of the ECG rather than QT prolongation, which may result from transmural dispersion in AP duration, in particular in the right ventricle, due to an early repolarization in the epicardial cell layers. On a cellular basis, a decrease in the peak component of I_{Na} due to a loss-of-function mutation in *SCN5A*, i.e. the gene encoding the pore-forming α subunit of the I_{Na} channel, may lead to loss of the AP dome in cells with a large transient outward current, like the right ventricular epicardial cells (Fig. 1B). It should be noted that this explanation of BrS as a

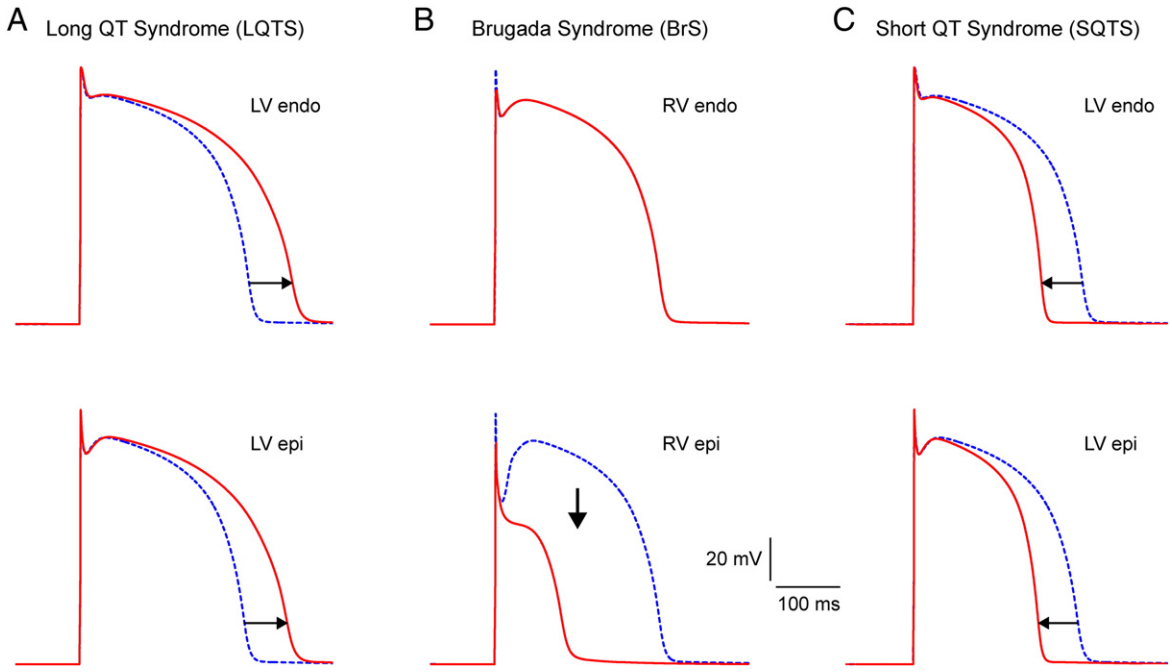

Fig. 1. Diagram of the left ventricular (LV) or right ventricular (RV) endocardial (endo) or epicardial (epi) action potential in case of (A) long QT syndrome, (B) Brugada syndrome, and (C) short QT syndrome. The dashed blue lines indicate control action potentials. Arrows mark the change in action potential configuration associated with the syndrome.

repolarization disease is a matter of debate and that it may also, or at the same time, be a depolarization disease [31]. In contrast with LQTS, the short QT syndrome is characterized by a shortening of the QT interval on the ECG and, at the cellular level, a shortening of the action potential (Fig. 1C). The shorter AP may result from gain-of-function mutations in genes related to outward currents that flow during the repolarization phase of the action potential, e.g. I_{Kr} and I_{Ks}. SQTS types 1 and 2 (SQT1 and SQT2) are caused by gain-of-function mutations in *KCNH2* (also known as *HERG*) and *KCNQ1* (also known as *KVLQT1*), which encode the α subunit of the I_{Kr} and I_{Ks} channel, respectively.

Since the proposal of LQTS as a possible cause of SIDS in 1976 [25,26], genetic or clinical correlations between LQTS and SIDS have been found in several studies. In 1998, Schwartz et al. [32] reported results from a 19-year electrocardiographic assessment of Italian neonates at day three or four of life. Of the 34,442 infants enrolled, one-year follow-up data were available for 33,034. In this cohort, 24 infants died of SIDS. Their mean rate-corrected QT interval (QTc) was significantly longer than that of infants who survived or died of other causes. More importantly, in 12 of them QTc was considered to be prolonged (>440 ms), whereas it was not in any of the 10 infants who died of other causes. It was found that the presence of QTc prolongation in the first week of life increased the risk of SIDS by 41 times. In 2000 and 2001, a number of case reports were published on mutations in LQTS genes in SIDS or near-SIDS [33–35], starting with the description by Schwartz et al. [33] of an infant who nearly died of SIDS and in whom LQTS was diagnosed and a spontaneous mutation in *SCN5A* was identified, providing a 'proof of concept' of cardiac ion channelopathies as a cause of SIDS. Shortly thereafter, Ackerman et al. [36] reported the results of the first population-based molecular study screening for mutations in LQTS genes as the possible cause of SIDS.

The findings by Schwartz et al. [32] initiated an ongoing discussion about the feasibility and relevance of neonatal electrocardiographic screening [37,38], identifying infants with LQTS and thus at risk for SIDS. In Italy, a large prospective ECG study in a population of 44,596 neonates was recently completed [39]. In 28 of the 29 infants with marked QT interval prolongation (QTc >470 ms), a molecular screening for mutations in any of the LQTS genes *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *CAV3* and *SCN4B*, associated with the LQTS types 1–3, 5, 6, 9 and 10, respectively, was performed. This revealed LQTS mutations in 12 neonates. Another three mutations were identified upon genetic analysis of 14 of the 28 neonates with a QTc between 461 and 470 ms. All but one, because of parental refusal, of the 29 neonates with a QTc >470 ms were successfully treated with a β-blocker (propranolol). It is tempting to speculate that this treatment has prevented the occurrence of SIDS in this group.

Postmortem genetic analysis of SIDS cases, screening for mutations in LQTS genes and related genes, has revealed associations of mutations in these genes with SIDS, as summarized in Table 1. This table is based on findings from population-based cohort studies and case reports. These findings are detailed in Sections 4.1–4.4 and summarized in Tables 2 and 3.

4.1. Cardiac potassium channel mutations

In 2005, more than 400 different LQTS-associated mutations had already been identified, the majority of which were localized in the I_{Ks} and I_{Kr} channel genes *KCNQ1* and *KCNH2*, underlying the LQTS types 1 and 2 (LQT1 and LQT2, respectively) [27,30]. Less frequently, defects are found in two other potassium channel genes, *KCNE1* (LQT5) and *KCNE2* (LQT6), which encode auxiliary β subunits of the I_{Ks} and I_{Kr} channel, respectively. These defects in potassium channel genes cause LQTS by reducing the repolarizing current carried by the specific potassium channel they encode, i.e. the I_{Ks} (*KCNQ1* and *KCNE1*) and the I_{Kr} channel (*KCNH2* and *KCNE2*). A number of LQTS-associated mutations in these potassium channel genes have been identified in SIDS cases. In addition, SIDS-related mutations in *KCNJ8*, encoding the pore-forming α subunit of the ATP-sensitive potassium channel, have recently been reported.

In their population-based collection of 93 unexplained infant deaths [36], Tester and Ackerman [40] screened for mutations in *KCNQ1*, *KCNH2*, *KCNE1* and *KCNE2*, and found novel potassium channel variants in *KCNQ1* (p.T600M), *KCNH2* (p.G294V) and *KCNE2* (p.V14I), as listed in Table 2. In addition, they also discovered a novel mutation in *KCNH2* (p.P1157L) following postmortem genetic testing in a separate case of an infant who was found dead in the prone sleep position (Table 3). None of these mutations was seen in nearly 1500

Table 1
Cardiac ion channel-related genes associated with SIDS.

Gene	Protein	Functional role in cardiomyocytes	Effect of mutation	Clinical syndrome
Potassium channel genes				
KCNQ1 (KVLQT1)	Kv7.1 (KvLQT1)	α subunit of I_{Ks} channel	I_{Ks} loss of function	LQT1
			I_{Ks} gain of function	SQT2
KCNE1	minK	β subunit of I_{Ks} channel	I_{Ks} loss of function	LQT5
KCNH2 (HERG)	Kv11.1	α subunit of I_{Kr} channel	I_{Kr} loss of function	LQT2
KCNE2	MiRP1	β subunit of I_{Kr} channel	I_{Kr} loss of function	LQT6
KCNJ8	Kir6.1	α subunit of $I_{K,ATP}$ channel	$I_{K,ATP}$ loss of function	–
Sodium channel genes				
SCN5A	Nav1.5	α subunit of I_{Na} channel	I_{Na} loss of function	BrS1
			I_{Na} gain of function	LQT3
SCN3B	Navβ3	β subunit of I_{Na} channel	I_{Na} loss of function	BrS7
SCN4B	Navβ4	β subunit of I_{Na} channel	I_{Na} gain of function	LQT10
Calcium channel genes				
RYR2	RyR2	Ryanodine receptor in SR membrane	Calcium leak from SR	CPVT1
Other genes				
CAV3	Caveolin-3	Caveolar coating	I_{Na} gain of function	LQT9
GPD1-L	G3PD1L	Not fully established	I_{Na} loss of function	BrS2
SNTA1	α1-syntrophin	Scaffolding protein	I_{Na} gain of function	LQT12
GJA1	Cx43	Gap junction protein	I_j loss of function	–

I_{Ks}: slow delayed rectifier potassium current; I_{Kr}: rapid delayed rectifier potassium current; $I_{K,ATP}$: ATP-sensitive potassium current; I_{Na}: fast sodium current; I_j: gap junctional current; LQT1–12: long QT syndrome types 1–12; SQT2: short QT syndrome type 2; BrS1–7, Brugada syndrome types 1–7; CPVT1: cathecholaminergic polymorphic ventricular tachycardia type 1.

reference alleles from healthy controls. However, there is no functional evidence, e.g. from in vitro expression studies, that any of these four mutations leads to potassium channel dysfunction and these are therefore not classified as 'functionally significant' in Tables 2 and 3. Furthermore, the *KCNQ1*-p.T600M and *KCNH2*-p.G294V variants occurred in the same black victim, together with the sodium channel variant *SCN5A*-p.S1103Y, which has later been associated with sudden infant death in African Americans [41] (see Section 4.2).

Wedekind et al. [42] performed a postmortem examination in a total of 41 SIDS cases of sudden and unexpected infant death, which occurred in 1991/1992 and 1995/1996 in the northwestern area of Germany. Apart from a number of common and rare polymorphisms, the results of screening for mutations in the LQTS genes *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1* and *KCNE2*, associated with the LQTS types 1–3, 5 and 6, respectively, were limited to a single missense mutation in *KCNQ1* (p.H105L). However, the mutant channel failed to display significant electrophysiological disturbances in vitro.

Between 1988 and 2004, Arnestad et al. [43] genetically analyzed 201 Norwegian cases of SIDS, screening for mutations in *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2* and *CAV3*, associated with LQTS types 1–3, 5–7 and 9, respectively. Mutations and rare variants in LQTS genes were identified in 26 cases. On the basis of the available functional data, 8 mutations and 7 rare variants found in 19 of 201 cases (9.5%) were considered as likely contributors to sudden death. In 11 cases, nine different mutations or rare variants in the potassium channel genes *KCNQ1* (5 cases), *KCNH2* (5 cases), and *KCNE2* (one case) were found (Table 2). No mutations were found in *KCNE1* or *KCNJ2*. However, one rare *KCNQ1* variant (p.P448R, three cases) appeared a common, ethnic-specific polymorphism [44], whereas the mutations p.V279M, p.R885C and p.S1040G in *KCNH2* (three cases in total) exhibited biophysical properties indistinguishable from wild-type [45] and are probably benign variants. For the remaining five cases clear functional effects have been found [43,45]. The functional characterization of the *KCNH2*-p.R273Q, *KCNH2*-p.R954C/p.K897T and *KCNE2*-p.Q9E mutations reveals a loss of function of the associated current (I_{Kr}), which would result in a long-QT phenotype. The functional effect of the *KCNQ1* mutations is a loss of function (p.G460S) or gain of function (p.I274V) of the associated current (I_{Ks}), which would result in a long-QT or short-QT phenotype, respectively.

In 2008, Otagiri et al. [46] reported the results of an investigation of 42 Japanese SIDS cases between 1995 and 2004. They studied the LQTS genes *KCNQ1*, *KCNH2* and *SCN5A* and identified two potassium channel mutations, one in *KCNQ1* (p.K598R) and one in *KCNH2* (p.T895M). The *KCNQ1*-p.K598R mutation did not noticeably alter the gating of *KCNQ1* channels expressed in oocytes and was therefore considered a rare polymorphism. However, this mutation has recently been identified as an LQT1 causing mutation in a clinical study [47]. Biophysical properties of *KCNH2*-p.T895M included a decrease in amplitude of the steady-state current and a delay in deactivation. Since these alterations seem to exert opposite functional effects, it is difficult to predict the overall in vivo effect of this mutation, especially as the subject it was found in also carried a defect in *SCN5A* (see Section 4.2).

Millat et al. [48] performed genetic screening of 32 French SIDS victims of Caucasian origin for mutations in *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1* and *KCNE2*, and found three potassium channel mutations, one in each of the genes *KCNQ1*, *KCNH2* and *KCNE1* (*KCNQ1*-p.G626S, *KCNH2*-p.R148W and *KCNE1*-p.T20I) and none in *KCNE2*. These mutations were interpreted by the authors as a possible cause of death. With regard to the *KCNQ1* mutation, some evidence is available to support this hypothesis [49]. However, the infant with the *KCNE1* mutation was also carrier of a spontaneous mutation in *SCN5A* that may provide a more likely explanation for her death, given that her father was found to be carrier of the *KCNE1*-p.T20I mutation with no LQTS-related phenotype [50]. The *KCNH2* defect is probably a benign polymorphism [51], as supported by the observation that the father, who also carried the mutation, was asymptomatic.

Recently, Tester et al. [52] performed a mutational analysis of *KCNJ8* on genomic DNA obtained from 292 unrelated SIDS victims. Two distinct and novel *KCNJ8* mutations were identified (p.E332del and p.V346I). Both cases were negative for mutations in established channelopathic genes. In vitro, both mutations resulted in a significant decrease in the associated ATP-sensitive potassium current ($I_{K,ATP}$). Loss of function of the *KCNJ8*-encoded cardiac K_{ATP} channel may result in a long-QT phenotype, predisposing to SIDS, but an isolated pro-arrhythmic mechanism remains speculative since *KCNJ8* is expressed in multiple tissues, including vascular and neuronal tissue [52].

In addition to the previously discussed cohort studies, a number of case reports are available in literature (Table 3). In 2001, Schwartz et al. [34] reported the identification of a de novo *KCNQ1* mutation (p.P117L), which was associated with clinical LQTS in an unrelated family, in an infant who died of SIDS. Additionally, a Scandinavian group found a novel mutation in *KCNH2* (p.K101E) in a seven-week-old SIDS victim [53]. Because of a positive family history for clinical LQTS and documented TdP, it was assumed that this mutation

Table 2
Cardiac ion channel-related mutations in population-based cohort studies of SIDS.

Gene	Study	Number of cases			Reported mutations*
		Total	With mutation	Functionally significant	
Potassium channel genes					
KCNQ1	Tester and Ackerman [40]	93	1	0	p.T600M
	Wedekind et al. [42]	41	1	0	p.H105L
	Arnestad et al. [43]	201	5	2	**p.I274V**, p.P448R (3 cases), **p.G460S**
	Otagiri et al. [46]	42	1	1	**p.K598R**
	Millat et al. [48]	32	1	1	**p.G626S**
	Total	*409*	*9 (2.2%)*	*4 (1.0%)*	
KCNE1	Tester and Ackerman [40]	93	0	0	–
	Wedekind et al. [42]	41	0	0	–
	Arnestad et al. [43]	201	0	0	–
	Millat et al. [48]	32	1	0	p.T20I
	Total	*367*	*1 (0.3%)*	*0*	
KCNH2	Tester and Ackerman [40]	93	1	0	p.G294V
	Wedekind et al. [42]	41	0	0	–
	Arnestad et al. [43]	201	5	2	**p.R273Q**, p.V279M, p.R885C, **p.R954C/p.K897T**, p.S1040G
	Otagiri et al. [46]	42	1	0	p.T895M
	Millat et al. [48]	32	1	0	p.R148W
	Total	*409*	*8 (2.0%)*	*2 (0.5%)*	
KCNE2	Tester and Ackerman [40]	93	1	0	p.V14I
	Wedekind et al. [42]	41	0	0	–
	Arnestad et al. [43]	201	1	1	**p.Q9E**
	Millat et al. [48]	32	0	0	–
	Total	*367*	*2 (0.5%)*	*1 (0.3%)*	
KCNJ2	Arnestad et al. [43]	201	0	0	–
KCNJ8	Tester et al. [52]	292	2 *(0.7%)*	2 *(0.7%)*	**p.E332del**, **p.V346I**
Sodium channel genes					
SCN5A	Ackerman et al. [36]	93	2	2	**p.A997S**, **p.R1826H**
	Wedekind et al. [42]	41	0	0	–
	Plant et al. [41]	133	7	7	**Homozygous p.S1103Y** (3 cases), **p.S524Y** (2 cases), **p.R689H**, **p.E1107K**
	Arnestad et al. [43]	201	13	13	**p.S216L**, **p.A586_L587del**, **p.R680H**, **p.R1193Q** (2 cases), **p.T1304M**, **p.F1486L**, **p.V1951L**, **p.F2004L** (3 cases), **p.P2006A** (2 cases)
	Otagiri et al. [46]	42	3	3	**p.F532C**, **p.G1084S**, **p.F1705S**
	Millat et al. [48]	32	3	1	p.Q692K, p.R975W, **p.S1333Y**
	Total	*542*	*28 (5.2%)*	*26 (4.8%)*	
SCN1B	Tan et al. [63]	292	0	0	–
SCN2B	Tan et al. [63]	292	0	0	–
SCN3B	Tan et al. [63]	292	2 *(0.7%)*	2 *(0.7%)*	**p.V36M**, **p.V54G**
SCN4B	Tan et al. [63]	292	1 *(0.3%)*	1 *(0.3%)*	**p.S206L**
Calcium channel genes					
RYR2	Tester et al. [73]	134	2 *(1.5%)*	2 *(1.5%)*	**p.R2267H**, **p.S4565R**
Other genes					
CAV3	Cronk et al. [77]	134	3	3	**p.V14L**, **p.T78M**, **p.L79R**
	Arnestad et al. [43]	201	3	2	p.C72W, **p.T78M** (2 cases)
	Total	*335*	*6 (1.8%)*	*5 (1.5%)*	
GPD1L	Van Norstrand et al. [79]	221	2 *(0.9%)*	2 *(0.9%)*	**p.I124V**, **p.R273C**
SNTA1	Cheng et al. [84]	292	8 *(2.7%)*	3 *(1.0%)*	p.G54R, p.P56S (3 cases), p.T262P, **p.S287R**, **p.T372M**, **p.G460S**
GJA1	Van Norstrand et al. [85]	292	2 *(0.7%)*	1 *(0.3%)*	**p.E42K**, p.S272P

*Functionally significant mutations listed in bold.

Table 3
Cardiac ion channel-related mutations in case reports of SIDS or near-SIDS.

Gene	Study	Findings	Reported mutation*
Potassium channel genes			
KCNQ1	Schwartz et al. [34]	De novo missense mutation identified in a case of SIDS	**p.P117L**
KCNH2	Christiansen et al. [53]	Novel missense mutation identified in a case of SIDS	**p.K101E**
	Tester and Ackerman [40]	Novel missense mutation identified in a case of SIDS	p.P1157L
	Nof et al. [54]	Common polymorphism (p.K897T) and nonsense mutation (p.P926AfsX14) on separate alleles identified in a case of sudden infant death and a case of spontaneous abortion within a single family	**p.P926AfsX14/p.K897T**
Sodium channel genes			
SCN5A	Schwartz et al. [33]	De novo missense mutation identified in a near-SIDS case with documented QTc prolongation, Torsades de Pointes and ventricular fibrillation	**p.S941N**
	Wedekind et al. [35]	De novo missense mutation identified in a case of sudden infant death with documented QTc prolongation and polymorphic ventricular tachyarrhythmias	**p.A1330P**
	Skinner et al. [65]	Missense mutation identified in a near-SIDS case with documented marginal QTc prolongation and ventricular fibrillation	**p.R1193Q**
	Turillazzi et al. [67]	Nonsense mutation identified in a case of simultaneous sudden infant death syndrome	**p.W822X**
	Huang et al. [50]	De novo missense mutation identified in a case of SIDS	**p.S1333Y**

*Functionally significant mutations listed in bold.

may well have caused a lethal arrhythmia. Finally, Nof et al. [54] presented a family in which an inherited common polymorphism in *KCNH2* (p.K897T) combined with a loss-of-function mutation (p.P926AfsX14) on separate alleles of the same gene led to sudden infant death and spontaneous abortion. Family members with only the polymorphism or only the mutation did not have any events of syncope or sudden cardiac death. Co-expression studies demonstrated a much greater loss of function of *KCNH2* current in case of p.P926AfsX14/p.K897T than for p.P926AfsX14 or p.K897T alone.

4.2. Cardiac sodium channel mutations

Gain-of-function mutations in the cardiac sodium channel gene *SCN5A* can cause LQTS, due to a persistent inward sodium current during myocardial repolarization [27]. Although defects in *SCN5A* account for only ≈10% of LQTS cases [55,56], this subtype (LQT3) does seem to play a rather important role in the etiology of SIDS. In general, it appears that patients with LQT3 have significantly more severe clinical events than patients with LQT1 or LQT2, as the overall number of cardiac deaths is similar for these subgroups while the frequency of events is lower in LQT3 [57]. Since the initial case report by Schwartz et al. [33], several *SCN5A* mutations have been identified in cohort studies of SIDS cases. In addition, a number of further case reports of an *SCN5A* mutation in a SIDS victim have been published.

Ackerman et al. [36] genetically analyzed postmortem cardiac tissue from 45 SIDS and 48 possible SIDS cases, obtained between September 1997 and August 1999 in the State of Arkansas, USA, for mutations in *SCN5A*. The same cohort was used in subsequent studies on ion channelopathies in relation to SIDS, e.g. the aforementioned study by Tester and Ackerman [40]. In two of these 93 cases, a missense mutation in *SCN5A* was found (p.A997S and p.R1826H). In either case, mutant channels expressed a sodium current characterized by slower decay and a two- to threefold increase in late sodium current, which would result in an LQT3 phenotype. As mentioned in Section 4.1, Wedekind et al. [42] also screened for mutations in *SCN5A* in their 41 German SIDS cases. However, they did not find mutations in this gene.

Plant et al. [41] studied the prevalence of *SCN5A* variants among 133 African American SIDS cases, and found homozygous and rare heterozygous *SCN5A* variants in seven cases (5%). Three cases were homozygous for p.S1103Y, a variant that had previously been associated with increased risk for arrhythmia in adults [58]. Comparison to controls gave an approximately 24-fold increase in risk of SIDS with the homozygous p.S1103Y genotype. In vitro, the variant p.Y1103 channels operated normally under baseline conditions, but showed abnormal function when subjected to lowered intracellular pH, which may indicate a predisposition to acidosis-induced arrhythmia. Three mutations in *SCN5A* at sites other than 1103 were identified in a total of four cases—p.S524Y (two cases), p.R689H, and p.E1107K—and characterized as gain-of-function mutations.

In the aforementioned study of 201 Norwegian SIDS cases by Arnestad et al. [43], nine *SCN5A* mutations or rare genetic variants were found in a total of 13 cases (6.5%). Biophysical characterization of the p.R1193Q variant [59] and the eight other mutations or rare variants [60] revealed an increased persistent sodium current in all cases, either under control conditions or only under conditions of internal acidosis (p.R680H) or when expressed in the context of the common splice variant p.Q1077del (p.A586_L587del and p.V1951L).

Mutations in *SCN5A* were also found in the aforementioned studies by Otagiri et al. [46] and Millat et al. [48]. In their 42 SIDS cases, Otagiri et al. [46] observed three mutations in *SCN5A* (p.F532C, p.G1084S and p.F1705S). In expression studies, the latter two showed hyperpolarizing shifts in inactivation (p.G1084S and p.F1705S) and a delayed recovery from inactivation (p.F1705S), loss-of-function features commonly seen in Brugada syndrome mutations in *SCN5A*. As for *SCN5A*-p.F532C, Otagiri et al. [46] found no evidence indicating a functionally perturbed channel in their expression experiments, but this mutation has recently been associated with the Brugada syndrome [61]. In their 32 SIDS victims, Millat et al. [48] also found three *SCN5A* mutations (p.Q692K, p.R975W and p.S1333Y). However, the first has wild-type like functional properties [62] and has recently been classified as a control variant [61], whereas the second is currently considered a rare control [51,61]. *SCN5A*-p.S1333Y causes a defect in inactivation with the presence of a residual current, comparable to LQT3 [50].

Tan et al. [63] screened their cohort of 292 SIDS cases for mutations in the four sodium channel β subunit genes *SCN1B* to *SCN4B*, and identified a total of three mutations in two of these genes (*SCN3B*-p.V36M, *SCN3B*-p.V54G and *SCN4B*-p.S206L). The two *SCN3B* mutations are both localized in the extracellular loop of the β subunit, which is important for β3 membrane trafficking. Compared with wild-type channels, p.V36M channels showed both loss-of-function and gain-of-function phenotypes in expression studies, i.e. decreased peak I_{Na} and increased late I_{Na} (at least when normalized to peak I_{Na}), respectively, whereas p.V54G was purely loss-of-function. *SCN4B*-p.S206L is associated with an increase in late sodium current, as demonstrated through adenoviral transduction of adult rat ventricular myocytes [63].

In addition to the previously mentioned cohort studies, a number of case reports on *SCN5A* mutations in SIDS or near-SIDS have been published (Table 3). In 2000, Schwartz et al. [33] reported a case of a 44-day-old boy with a normal clinical and family history, who had suddenly gone into ventricular fibrillation. After successful defibrillation the infant was diagnosed with LQTS, and subsequent genetic testing demonstrated a de novo missense mutation in *SCN5A* (p.S941N) with an increase in late sodium current. The p.A1330P protein change is another *SCN5A* defect described in a case report of sudden infant death [35]. Functional analysis of this mutation showed a positive shift in voltage dependence of inactivation, a slowing of the time course of inactivation, and faster recovery from inactivation [35]. A direct demonstration of the mutation effects on the action potential was obtained in 'dynamic action potential clamp' experiments by Berecki et al. [64]. In 2005, Skinner et al. [65] reported a near-SIDS case of a 19-day-old infant. Genetic analysis revealed a missense mutation in *SCN5A* (p.R1193Q) that had been associated with the Brugada syndrome in a previous study [66]. This mutation was also found in the SIDS cohort of Arnestad et al. [43] and characterized as an LQT3 mutation by Wang et al. [59]. In another case report [67], the heterozygous p.W822X nonsense mutation in *SCN5A* was linked to the death of both members of a set of monozygotic healthy twins ('simultaneous sudden infant death syndrome', SSIDS). This mutation had been linked to the Brugada syndrome in a previous study [68]. Finally, there is a case report on a de novo p.S1333Y mutation in *SCN5A* identified in a SIDS victim who also carried the p.T20I mutation in *KCNE1* [50]. This SIDS victim appears as case 46 in the study by Millat et al. [48]. In addition to these case reports, Priori et al. [69] reported on two cases of SIDS in a family with Brugada syndrome and the p.L567Q mutation in *SCN5A*, which was later functionally characterized as a loss-of-function mutation by Wan et al. [70]. Although direct genetic data of the two victims are not available, it is likely that they carried the familial p.L567Q mutation.

4.3. Cardiac calcium channel mutations

Cathecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disorder, characterized by adrenergically mediated polymorphic ventricular tachyarrhythmias in the absence of electrocardiographic markers and structural heart disease [71]. CPVT1 is the autosomal dominant form of the disease, caused by mutations in the *RYR2*-encoded cardiac ryanodine receptor that is located in the membrane of the sarcoplasmic reticulum (SR). This

channel is responsible for the process of calcium-induced calcium release, which is triggered by the small rise in intracellular calcium through activation of voltage sensitive L-type calcium channels upon membrane depolarization.

A 2004 study from the Mayo Clinic represented the first 'molecular autopsy' of *RYR2* in cases of sudden unexplained death [72]. In the cohort of 49 cases, six distinct *RYR2* missense mutations were found in seven cases (14%). Next, Tester et al. [73] performed a study with the aim to determine the spectrum and prevalence of *RYR2* mutations in a cohort of 134 SIDS cases. Overall, two distinct and novel *RYR2* mutations (p.R2267H and p.S4565R) were identified in two cases of SIDS that were subsequently established to be mutation-negative for all known LQTS susceptibility genes. Both amino acid substitutions were absent in 400 reference alleles. Functional characterization showed that the two mutant channels were prone to display a significant gain-of-function 'leaky' phenotype, especially under conditions that simulate stress during diastole. These findings are supported by the recent study by Mathur et al. [74], who created a knock-in mouse model of SIDS and reported that young mice with the gain-of-function mutation p.R176Q in *RYR2* [75] show an increased propensity to calcium leak-induced cardiac arrhythmias and sudden death. The nocturnal occurrence of cardiac arrhythmias in SIDS can be explained by sudden increases in sympathetic activity, for example following hypoxia or possibly even during REM sleep [73].

4.4. Other cardiac ion channel-related mutations

The cardiac fast sodium channel is localized in caveolae, membrane microdomains involved in vesicular trafficking, whose major component in cardiomyocytes is *CAV3*-encoded caveolin-3 [76]. Vatta et al. [76] reported a novel type of the long QT syndrome (LQT9) associated with mutations in *CAV3* that result in a two- to threefold increase in late sodium current compared with wild-type caveolin-3, similar to the functional effect of LQT3-associated *SCN5A* mutations. Cronk et al. [77] investigated the prevalence of LQT9 in 134 cases of SIDS, and identified three distinct *CAV3* mutations (p.V14L, p.T78M and p.L79R). At functional characterization, all of these showed a significant ≈5-fold increase in late sodium current, consistent with the LQT3-like phenotype described by Vatta et al. [76]. In their population of 201 Norwegian SIDS cases, Arnestad et al. [43] also identified two *CAV3* variants (p.C72W and p.T78M). Since p.T78M had earlier been characterized as a functionally significant mutation [77], this variant was considered pathogenic, although one of the two victims with this variant also carried the functionally significant p.A586_L587del mutation in *SCN5A*. With regard to p.C72W, no functional data are available. Of note, the p.C72W variant had actually been designated as a common polymorphism in the original study identifying *CAV3* as the LQT9 locus [76].

London et al. [78] reported that the p.A280V mutation in the gene *GPD1-L*, encoding the glycerol-3-phosphate dehydrogenase 1-like protein (G3PD1L), reduced inward sodium current and thus caused Brugada syndrome. Given this finding, Van Norstrand et al. [79] analyzed 83 cases of sudden unexplained death, including 7 SIDS cases, and identified a *GPD1-L* mutation in a 3-month-old boy (p.E83K). Further analysis of a cohort of 221 SIDS cases revealed two additional mutations (p.I124V and p.R273C). All three mutations were absent in 600 reference alleles. Compared with wild-type, coexpression of mutant *GPD1-L* with *SCN5A* resulted in a significantly reduced sodium current, consistent with a loss-of-function, BrS-like phenotype. London et al. [78] found a reduced cell surface expression of *SCN5A* with mutant *GPD1-L* and hypothesized that the mutation caused impaired trafficking of the cardiac sodium channel to the cell surface. Valdivia et al. [80] later provided evidence that the effect of the mutation in *GPD1-L* is through a reduced enzymatic function of G3PD1L, which regulates *SCN5A* through direct phosphorylation, whereas another study [81] emphasizes the role of a mutation-induced increase in the intracellular concentration of NADH.

In 2008, Ueda et al. [82] and Wu et al. [83] almost simultaneously reported that mutations in *SNTA1*, encoding α1-syntrophin, may lead to LQTS through a gain of function of the fast sodium channel, as in LQT3. Ueda et al. [82] found that the p.A390V mutation led to LQTS through increased direct S-nitrosylation of the cardiac sodium channel, resulting in a marked increase in late sodium current. The increase in late sodium current was accompanied by an increase in peak sodium current, an increase in sodium channel availability through a +6 mV shift in sodium channel inactivation, and a slower time course of sodium current decay. Wu et al. [83] studied the p.A257G mutation in *SNTA1* and also found an increase in late sodium current, due to an increase in peak sodium current, an increase in sodium channel availability through a –9 mV shift in sodium channel activation, and a slower time course of sodium current decay. Subsequently, Cheng et al. [84] investigated the prevalence and functional properties of *SNTA1* mutations in a cohort of 292 SIDS cases. Six mutations were found in eight cases, with one particular mutation (p.P56S) identified in three cases, and were absent in 800 reference alleles. In vitro, a significant increase in peak and late sodium current was observed for p.S287R, p.T372M and p.G460S, which was reversed by a neuronal nitric oxide synthase inhibitor. The other three variants (p.G54R, p.P56S and p.T262P) showed functionally insignificant changes in the sodium current.

Recently, Van Norstrand et al. [85] detected two novel missense mutations (p.E42K and p.S272P) in *GJA1*, i.e. the gene that encodes the gap junction channel protein connexin43 (Cx43), in their cohort of 292 SIDS cases. Functional studies were performed using dual whole cell patch-clamp and revealed a strongly reduced gap junctional conductance for p.E42K compared to wild-type. Such strongly reduced intercellular coupling may result in lethal ventricular arrhythmias, as demonstrated in several conditional Cx43 knockout models [86].

5. Prevalence of cardiac ion channelopathies in SIDS

The data from the population-based cohort studies summarized in Table 2 allow us to calculate the prevalence of cardiac ion channelopathies among SIDS victims. In our calculations we ignore that a few SIDS victims carried more than one ion channel-related mutation, as described in Section 4, and thus appear in Table 2 more than once. This holds for the infant from the study by Tester and Ackerman [40] with the *KCNQ1*-p.T600M and *KCNH2*-p.G294V variants, the infant from the study by Millat et al. [48] with the *KCNE1*-p.T20I and *SCN5A*-p.S1333Y mutations, and the infant from the study by Arnestad et al. [43] with the *CAV3*-p.T78M and *SCN5A*-p.A586_L587del mutations. Furthermore, by merging data from different studies, we ignore differences in the underlying populations, which are mostly from North American origin, but also from African American [41], German [42], Norwegian [43], French [48] and Japanese [46] origin.

First, we can calculate that 19.5% of the SIDS victims carried a mutation in any of the 16 cardiac ion channel-related genes studied and that there is evidence for malignancy of these mutations in the majority of cases (13.5%). In a minority of cases (6.0%), as detailed in Section 4, there are either no data on the functional effects of the mutation or no functionally significant effects have been observed, e.g. in expression studies. In the latter case, there may still be latent functional defects that are not evident under the conditions of the functional test. For example, there may be defects that only show their malignancy in case of acidosis or in the context of a specific splice variant, as for some of the SIDS associated *SCN5A* variants studied by Wang et al. [60] (see Section 4.2). Another example is the SIDS associated *KCNQ1*-p.K598R mutation, which seemed benign when expressed in oocytes [46], but was later identified as an LQT1 causing mutation in a clinical study [47] (see Section 4.1). Another factor that may turn apparently benign mutations into malignant ones is high

temperature. The malignant properties of a mutation may become more severe with an increase in temperature, as demonstrated for several sodium channel mutations associated with the Brugada syndrome, e.g. in the studies by Dumaine et al. [87] and Keller et al. [88], explaining fever-induced arrhythmias observed in BrS patients. Recently, Amin et al. [89] demonstrated that fever is also a potential trigger of life-threatening arrhythmias in the long QT syndrome. Although direct evidence is lacking, arrhythmogenic events triggered by high body temperature may also play a role in the etiology of SIDS.

So the prevalence of malignant cardiac ion channel-related mutations among SIDS victims may actually be close to 20%. It may even be higher, given that conventional genetic analysis may fail to uncover severe mutations [90,91] and that the determination of associations between SIDS and mutations in ion channel-related genes is still an emerging field, with several associations that have only recently been reported [52,63,85] and others that remain to be tested, e.g. a possible association between SIDS and mutations in the ankyrin-B encoding gene *ANK2*, leading to the ankyrin-B syndrome and LQT4 [30]. Of note, the prevalence of LQTS and BrS associated mutations among SIDS victims is much higher than the estimated prevalence of 1:2000 for both LQTS and BrS in the general population [29,30].

Second, we can conclude that mutations in I_{Na} channel related genes are the most malignant ones. Mutations in the α subunit encoding gene, *SCN5A*, are found in 5.2% of the SIDS victims (Table 2), in accordance with the observation in adults that LQT3 has the most severe clinical events [57] and that these events tend to occur during sleep [92], as in SIDS. In total, more than half of the reported mutations are related to the I_{Na} channel. In addition to the mutations in *SCN5A*, there are mutations in the β subunit encoding genes *SCN3B* and *SCN4B* (1.0%) and in 'regulatory genes' (*CAV3*, *GPD1-L* and *SNTA1*; 5.4%), adding up to a prevalence of 11.6% for mutations affecting I_{Na}, with functional evidence available for 9.2% (Table 2). Similar percentages for the 'cardiac sodium Nav1.5 channelsome' have recently been reported by Van Norstrand et al. [93]. With a total prevalence of 5.7%, with functional evidence in case of 2.7%, mutations in potassium channel genes (*KCNQ1*, *KCNE1*, *KCNH2*, *KCNE2*, *KCNJ2* and *KCNJ8*) seem less frequent and less malignant.

6. Concluding remarks

In this review, we show that a considerable number of SIDS victims, although they may have appeared healthy during their lives, do in fact display genetic variants that are associated with clinical disorders. Various mechanisms have been hypothesized or already proven to play a role in the etiology of SIDS. In particular, mutations in cardiac ion channel-related genes are of importance. Data from population-based cohort studies suggest that cardiac ion channelopathies are present in at least 20% of SIDS cases. Genetic analysis for these and other mutations is therefore recommended in cases of sudden infant death. However, more research is required to further elucidate the pathophysiology of SIDS, and to determine whether genetic or electrocardiographic screening of apparently healthy infants should be pursued.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publications in the International Journal of Cardiology [94].

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